METHODS AND COMPOSITIONS FOR TREATING VIRAL INFECTIONS

FIELD

[0001] Disclosed herein are methods and compositions for treating viral infections.

BACKGROUND

[0002] Viruses are obligatory intracellular parasites. Animal viruses must cross the host boundary for cell entry and exit. In enveloped viruses, this occurs by fusion of the incoming virus with, and budding of the nascent virus through a cellular membrane. In nonenveloped viruses, virus entry requires transient disturbance of a cellular (mostly endosomal) membrane to transfer the viral genome into the cytoplasm. Intracellularly, viruses induce cytoplasmic membrane structures and compartments, in which genome replication and assembly occurs.

[0003] Viral infections account for large fraction of infectious disease mortality and morbidity worldwide. Cytomegalovirus (CMV), for example, is a beta herpesvirus; it is a major cause of morbidity and mortality in immunocompromised individuals, including AIDS patients and recipients of hematopoietic stem cell transplantation (HSCT) or solid organ transplants, cancer patients, and patients at intensive care. CMV is also the leading cause of congenital infection, affecting about 1% of live births, with resultant neurological damage and loss of hearing. Despite the considerable public health burden of congenital CMV, no established prenatal antiviral treatments are available.

[0004] Acquired immunodeficiency syndrome (AIDS) is the result of infection by human immunodeficiency virus (e.g., HIV-1). HIV continues to be a major global public health issue. Current therapy for HIV-infected individuals typically consists of a combination of approved anti-retroviral agents. Over two dozen drugs are currently approved for HIV infection, either as single agents or as fixed dose combinations or single tablet regimens. Despite the armamentarium of agents and drug combinations, there remains a medical need for new anti-retroviral agents, due in part to the need for chronic dosing to combat infection. Significant problems related to long-term toxicities are documented, creating a need to address and prevent these co-morbidities.

[0005] HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The HCV virion contains a positive-stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids (AA). The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B. Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin, which exhibits substantial limitations to efficacy and tolerability. There is a need for new therapies to treat HCV infection.

[0006] HBV infection is a major public health problem, affecting approximately 2 billion people worldwide. Among them, 350 million people worldwide and 1.4 million in the US develop a chronic infection, which can lead to chronic persistent hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Every year hundreds of thousands of people die from end stage liver disease caused by HBV infection. The burden of chronic HBV infection continues to be a significant unmet worldwide medical problem, due to suboptimal treatment options and sustained rates of new infections in most parts of the developing world.

[0007] Herpes simplex virus (HSV) is a neurotropic pathogen, and transits to sensory nerves after initial infection into mucosal epithelium, then latently infects for a lifetime at trigeminal ganglion or sacral ganglion. Latent HSV sometimes reactivates, causing a variety of pathologies. Two serotypes (HSV-1, HSV-2) are known for HSV. HSV-1 predominantly causes lip/corneal herpes, and HSV-2 predominantly causes genital herpes. Antiviral therapies against these viruses are sorely lacking.

[0008] Dengue virus (DENV) is one of the most significant mosquito-borne viral infections affecting humans today and is an NIAID Category A Biodefense pathogen. DENV is a plus-stranded RNA virus and a member of the Flaviviridae family. The 4 Dengue virus serotypes (DENV1, DENV2, DENV3, and DENV4) are defined by the viral envelope protein (E) and share 60% sequence homology at the AA level.

[0009] Filoviruses (e.g., Ebola virus (EBOV) and Marburg virus (MARV)) are among the most lethal and destructive viruses. They cause severe, often fatal viral hemorrhagic fevers in humans and nonhuman primates (e.g., monkeys, gorillas, and chimpanzees). Filoviruses are of particular concern as possible biological weapons since they have the potential for aerosol dissemination and weaponization.

SUMMARY

[0010] Provided herein are methods and compositions for treating viral infections, comprising administration of placental adherent stromal cells (ASC), and conditioned media (CM) thereof.

[0011] Conditioned medi[a]/[um]/CM, as used herein, refers to a growth medium that has been used to incubate a cell culture. The present disclosure is not intended to be limited to particular medium formulations; rather, any medium suitable for incubation of placental ASC is encompassed.

[0012] In certain embodiments, the described placental ASC have been cultured on a 2-dimensional (2D) substrate, a 3-dimensional (3D) substrate, or a combination thereof. Non-limiting examples of 2D and 3D culture conditions are provided in the Detailed Description and in the Examples.

[0013] Alternatively or in addition, the placental ASC are allogeneic to the subject; or, in other embodiments, are autologous; or, in other embodiments, are xenogeneic

[0014] Reference herein to "growth" of a population of cells is intended to be synonymous with expansion of a cell population. In certain embodiments, ASC (which may be, in certain embodiments, placental ASC), are expanded without substantial differentiation. In various embodiments, the described expansion is on a 2D substrate, on a 3D substrate, or a 2D substrate, followed by a 3D substrate.

[0015] Except where otherwise indicated, all ranges mentioned herein are inclusive.

[0016] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar